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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,066	12/07/2001	John J. L. Simard	0088480-021US1	8425

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/19/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/026,066	SIMARD ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,29-36,40-52 and 54-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,29-36,40-52 and 54-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner of your application in the PTO has changed. The prior rejections of record stand as enunciated below.

2. Applicant's amendment filed 1/19/10 is acknowledged and has been entered.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-5, 29, 30, 33-35 and 40-41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zajac *et al* (145 on form PTO-1449; Int. J. Cancer [1997] 71:491-496, of record) in view of Kawakami *et al* (J. Immunother. [1998] 21(4):237-246; 77 on form PTO-1449 filed 12/9/2002).

Zajac *et al* teaches isolated T cells that recognize the HLA-A2.1-restricted housekeeping epitope consisting of amino acid residues 27-35 of the MelanA tumor-associated antigen from melanoma target cells (Abstract and page 491, first column in particular) [claims 1, 3, 29, 30, 33-35]. Zajac teaches that tumor-infiltrating-lymphocytes (TILs) were isolated from melanoma patients were able to specifically lyse target cells (pages 492-493 and Figure 2 in particular). Zajac *et al* discusses the use of the MART-1/MelanA27_35 peptide as an active immunogen in cancer patients (Abstract and page 495, column 2 in particular).

Claims 40 and 41 are included because a blood sample obtained from a human subject would easily have comprised between 10^5 and 10^{11} T cells in total.

Zajac *et al* does not teach expansion of tumor-reactive T cells in *in vitro* culture and making the cells suitable for administration as an adoptive immunotherapeutic reagent.

Kawakami *et al* teaches that "[t]umor-reactive T cells that have been activated in vivo can then be further expanded by in vitro culture with IL-2 and used for adoptive immunotherapy" (page 239, second column in particular).

Accordingly, it would have been well within the purview of the artisan at the time the invention was made to expand tumor-reactive T cells in *in vitro* culture and make the cells suitable for administration as an adoptive immunotherapeutic reagent.

Like Zajac *et al*, Kawakami *et al* also discusses the use of the MART-1/MelanA27-35 peptide as an active immunogen, referring to clinical protocols (Table 4 in particular).

However, Kawakami *et al* also teaches that potent melanoma-reactive T cells can be induced from the peripheral lymphocytes of cancer patients or from subjects immunized with the peptides [claim 5] and useful for adoptive transfer protocols (page 242, column 2 to page 243, column 1 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use expanded T cells from the cells or isolated T cells of Zajac *et al* as an adoptive immunotherapeutic.

One would have been motivated to formulate a therapeutic preparation suitable for use in humans comprising these cells with a reasonable expectation of success by the teachings of Kawakami that cells expanded in vitro with substances such as IL-2 can still be used for adoptive transfer to human subjects.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record in the amendment and response filed 1/19/10 on pages 8-12 at section A.

First Applicant is arguing the references separately in arguing that the T cells derived by Zajac *et al* are not suitable for adoptive transfer to a human because of exposure to agents that would be present in the composition, and that there is no teaching or suggestion to use the TILS for any purpose beyond assessing the properties of the reagent disclosed therein.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The instant rejection combines the teachings of two references to arrive at a composition that is suitable for adoptive transfer to a human. In addition, Kawakami *et al* teach that CTL specific for a tumor associated antigenic peptide can be expanded in vitro culture with IL-2 and used for immunotherapy, thereby providing motivation for adoptive therapy.

With regard to Applicant's argument about the limitation ""wherein said T cell is isolated from an immunized animal", the art meets the claim limitation as the T cell is isolated from an immunized animal, *i.e.,* one immunized with the tumor *in vivo*, and then restimulated *in vitro*.

With regard to Applicant's argument about the issue of deriving the combination of references to arrive at an adoptive immunotherapeutic reagent comprising a T cell specific for *a housekeeping epitope* from the instant specifcation is off-point, as is Applicant's argument about inherency analysis.

The claims are directed to a product. There is motivation to combine the references to arrive at the claimed product. The later discovery of an unknown characteristic or property of a known compound, *i.e.,* in this case, that the epitope is a housekeeping epitope, does not by itself render said product patentable.

"Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. " The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art". Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

With regard to Applicant's argument about an inherency analysis, the formerly unknown property of the art epitope being a housekeeping epitope, is not part of the obviousness analysis, nor the reason to combine the references, contrary to Applicant's implication to the contrary.

Applicant's further argument about intermediate products is also off-point. The art references provide the motivation and teaching to produce the claimed invention with a reasonable expectation of success, as enunciated supra.

2. Claims 1-5, 29, 30, 33, 34, 36 and 40-41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kittlesen *et al* (79 on form PTO-1449; J. Immunol. [1998] 160:2099-2106, of record) in view of Kawakami *et al* (J. Immunother. [1998] 21(4):237-246; 77 on form PTO-1449 filed 12/9/2002, newly cited).

Kittlesen *et al* teaches isolated T cell lines that recognize the HLA-Al-restricted housekeeping epitope consisting of the amino acid sequence KCDICTDEY of the tyrosinase tumor-associated antigen from melanoma target cells (Abstract, page 2100, first column in particular, page 2101, second column in particular)[claims 1, 29, 30, 33, 34, 36]. Kittlesen*et al* teaches that the tyrosine reactive T cells are obtained from melanoma patients whose tumors express tyrosinase (paragraph bridging pages 2100-2101 in particular) and therefore qualify as being "isolated from an immunized animal" because they were obtained from melanoma patients and were therefore "immunized" to the antigen by the presence of the tumor in their body [claim 5]. Accordingly, prior to transformation of the cell line the reactive T cells were present in human serum, a carrier suitable for administration to a human. The composition satisfies the metes and bounds of the claimed composition. Kittlesen *et al* further teaches that the T cell lines

were enriched *in vitro* from polyclonal populations [claim 3] obtained from melanoma patients by repeated rounds of stimulation with the peptide (page 2100, first column in particular) [claims 2, 4].

Claims 40 and 41 are included because a blood sample obtained from a human subject would easily have comprised between 10^5 and 10^{11} T cells in total.

Kawakami *et al* teaches that "[t]umor-reactive T cells that have been activated in vivo can then be further expanded by in vitro culture with IL-2 and used for adoptive immunotherapy" (page 239, second column in particular).

Accordingly, it would have been well within the purview of the artisan at the time the invention was made to expand tumor-reactive T cells in *in vitro* culture and make the cells suitable for administration as an adoptive immunotherapeutic reagent. Like Kittlesen *et al*, Kawakami *et al* also discusses the use of the peptide epitopes as an active immunogen, referring to clinical protocols (Table 4 in particular). Furthermore, Kawakami also discloses the generation oft cells reactive with tyrosinase epitopes (table 3 in particular). Kawakami *et al* also teaches that potent tumor-reactive T cells can be induced from the peripheral lymphocytes of cancer patients or from subjects immunized with the peptides [claim 5] and useful for adoptive transfer protocols (page 242, column 2 to page 243, column 1 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use expanded T cells from the cells isolated T cells of Kittlesen *et al* as an adoptive immunotherapeutic.

One would have been motivated to formulate a therapeutic preparation suitable for use in humans comprising these cells with a reasonable expectation of success by the teachings of Kawakami *et al* that cells expanded *in vitro* with substances such as IL-2 can still be used for adoptive transfer to human subjects.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record in the amendment and response filed 1/19/10 on page 13 at section B.

Applicant invokes the argument that the same reasons cited in "A" above, apply herein.

The Examiner's response to said arguments thereto pertain herein.

Again, Applicant is arguing the references separately. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The instant rejection combines the teachings of two references to arrive at a composition that is suitable for adoptive transfer to a human. In addition, Kawakami *et al* teach that CTL specific for a tumor associated antigenic peptide can be expanded in *in vitro* culture with IL-2 and used for immunotherapy, thereby providing motivation for adoptive therapy.

With regard to Applicant's argument about no [anti-]tyrosinase activity reported for T cells directly obtained from melanoma patients, [and the limitation ""wherein said T cell is isolated from an immunized animal"], the art meets the claim limitation as the T cell is isolated from an immunized animal, *i.e.*, one immunized with the tumor *in vivo*, and then restimulated *in vitro*.

Furthermore, in arguing "frequency" and "activated in vivo", Applicant is arguing non-recited limitations.

3. Claims 1-5, 29-32, 35 and 40-41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Jager *et al* (75 on form PTO-1449; J. Exp. Med. [1998] 187:265-270, of record) in view of Kawakami *et al* (J. Immunother. [1998] 21(4):237-246; 77 on form PTO-1449 filed 12/9/2002, newly cited).

Jager *et al* teaches isolated CD4+ T cell lines and an HLA-A2 restricted CTL clonal line that recognize housekeeping epitopes of the NY-ESO-1 cancer-testis tumor-associated antigen (Abstract and page 266, first column in particular)[claims 1-3, 29-32, 35]. Jager *et al* teaches that the NY-ESO-1 reactive T cells are obtained from PBL from a melanoma patient. Jager *et al* teaches that the T cells are obtained from a melanoma patient and therefore qualify as being "isolated from an immunized animal" because they were obtained from a melanoma patient that was therefore "immunized" to the antigen by the presence of the tumor in the body [claim 5].

Claims 40 and 41 are included because a blood sample obtained from a human subject would easily have comprised between 105 and 1011 T cells in total.

Kawakami *et al* teaches that "[t]umor-reactive T cells that have been activated in vivo can then be further expanded by in vitro culture with IL-2 and used for adoptive immunotherapy" (page 239, second column in particular). Accordingly, it would have been well within the purview of the artisan at the time the invention was made to expand tumor-reactive T cells in in vitro culture and make the cells suitable for administration as an adoptive immunotherapeutic reagent. Jager *et al* teaches that NY-ESO- 1 peptide can be used as an active immunogen as a vaccine preparation (page269, column 2 in particular). Kawakami *et al* also discusses the use of peptide epitopes as an active immunogen, referring to clinical protocols (Table 4 in particular). Kawakami *et al* also teaches that potent tumor-reactive T cells can be induced from the peripheral lymphocytes of cancer patients or from subjects immunized with the peptides [claim 5]

and useful for adoptive transfer protocols (page 242, column 2 to page 243, column 1 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use expanded T cells from the cells isolated T cells of Jager *et al* as an adoptive immunotherapeutic. One would have been motivated to formulate a therapeutic preparation suitable for use in humans comprising these cells with a reasonable expectation of success by the teachings of Kawakami *et al* that cells expanded in vitro with substances such as IL-2 can still be used for adoptive transfer to human subjects.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record in the amendment and response filed 1/19/10 on pages 13-14 at section C.

Applicant invokes the argument that the same reasons cited in "A" and "B" above, apply herein.

The Examiner's response to said arguments thereto pertain herein.

4. Claims 45-52 and 54-59 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zajac *et al* (145 on form PTO-1449; Int. J. Cancer [1997] 71:491-496, of record) in view of Kawakami *et al* (J.Immunother. [1998] 21(4):237-246; 77 on form PTO-1449 filed 12/9/2002, newly cited), Jager *et al* (75 on form PTO-1449; J. Exp. Med. [1998] 187:265-270, of record) and Tsuji *et al* (Int. J. Immunopharmacology [1998] 20(1-3): 111--124 (newly cited; U on form PTO-892).

Zajac*et al*, Kawakami *et al* and Jager *et al* have been discussed supra.

The references each teach the generation of T cells specific for tumor associated antigens in melanoma patients [claims 42, 44-47]. Zajac *et al* specifically teaches the generation ofA2-restricted T cells reactive with the melanoma differentiation antigen Melan-A [claims 50-52]. Jager *et al* specifically teaches the generation of T cells specific for the cancer-testis antigen NY-ESO [claims 48, 49]. Kawakami teaches the in vitro generation of T cell clones suitable for adoptive administration to a human [claim 43].

The combined references do not specifically teach immunizing a subject against more than one epitope.

Tsuji *et al* teaches immunizing a subject with multiple peptides derived from B 16 melanoma cells (Abstract in particular). Tsuji teaches that the peptides were acid eluted from cultured tumor cells, acid elution removes peptides from MHC class I on the surface of the cells (page 112 in particular), meaning that these peptides from non-immune cells are the product of processing by standard proteasomes and therefore are

housekeeping epitopes. As these peptides are derived from whole cell elutions, the preparations comprise housekeeping epitopes from both different antigens (claims 45-52) and from same antigens (claims 54-59) of the tumor cells.

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to treat a subject with T cells specific for more than one housekeeping epitope at the same time when the housekeeping epitopes are derived from the same or different antigens of the tumor.

One of ordinary skill in the art would have been motivated to combine the teachings for such a combination therapy with a reasonable expectation of success by the teachings of Tsuji showing that treating a subject with multiple peptides inhibited tumor growth and promoted survival of treated subjects, and by the fact that not only do both Zajac and Jager *et al* teach the expansion of housekeeping epitope specific T cells *in vitro*, which Kawakami *et al* teach can be expanded for adoptive immunotherapy, but they also teach the use of these peptides for active therapy in subjects, providing a nexus to the peptide therapy taught by Tsuji.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record in the amendment and response filed 1/19/10 on pages 14-15 at section "D".

One of ordinary skill would have had the motivation to combine the references to produce the claimed invention with a reasonable expectation of success for the reasons enunciated supra, and also because Kittleson *et al* teach (especially paragraph spanning pages 2099-2100) that multiple TAA proteins such as Melan-A taught by Zajac *et al* and tyrosinase taught by Kawakami *et al* are expressed in the vast majority of human melanomas, and both Zajac *et al* and Kawakami *et al* teach HLA-A2-binding CTL epitope peptides, for the TAA proteins, respectively,

With regard to Applicant's arguments about the B16 melanoma line taught by Tsuji *et al*, Applicant argues that multiple components of the MHC class I antigen processing pathway are defective in this cell line, and consequently one would not have looked to Tsuji cell line as a source of epitopes to treat clinical as opposed to model tumors, nor gives guidance that these are the epitopes that one should target in adoptive immunotherapy. Applicant asserts that one would have been disinclined to look to the Tsuji cell lines as a source of desirable epitopes or T cells.

However, the instant rejection is not predicated upon using the peptides from the B16 melanoma tumor cell line of Tsuji, but rather using T cells specific for more than one epitope, such as the T cells and epitopes taught by Zajac *et al* (from Melan-A TAA protein) and by Kawakami *et al* (from tyrosinase TAA protein). Tsuji is cited for the teaching that the endogenously presented peptides eluted from the said melanoma cell

line contain epitopes from both different antigens and from the same antigens present in the tumor cell line.

In addition, the references are being argued separately by Applicant.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The instant rejection stands for the reasons of record, and for those enunciated herein.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Ram R. Shukla/

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